REMARKS

Applicants respectfully request the Examiner to reconsider the present application in view of the foregoing amendments to the claims and specification and the following remarks.

Status of the Claims

Claims 1, 2 and 5-27 are currently pending in the present application. The Office Action is non-final. Claims 12-21 and 23-26 are withdrawn from consideration as being directed to a non-elected invention. Claims 1, 5, 6, 22 and 23 have been amended while claims 3-4 have been cancelled without prejudice or disclaimer of the subject matter contained therein. Claim 27 is new. No new matter has been added by way of the amended or new claims. For instance, claim 1 has been amended to include subject matter taken from claim 4, now cancelled. Support for claim 5 can be found in original claim 1 and page 12, line 25 of the present specification. Support for claims 22 and 23 can be found on page 28, lines 10-13, and page 32, lines 9-11 of the present specification. Support for new claim 27 can be found in original claim 5 and page 12, lines 22-26 of the present specification. Thus no new matter has been added.

With regards to the specification, the specification was amended at page 30, lines 2-14, to correct the typographical error "CUGA" to "CUAG" within the paragraph. Further, the specification was amended on page 30, lines 19-28, to correct an inadvertent transposition of SEQ ID NOs: 14 and 15 with regards to their respective RNA. Thus, no new matter has been added.

Based upon the above considerations, entry of the present Amendment is respectfully requested.

Objection to the Specification

The Examiner objects to the specification due to informalities (See page 3 of the Office Action dated November 21, 2008; hereinafter "Office Action").

Applicants herein provide amendments to the specification that resolve the above informalities. Applicants corrected the typographical error "CUGA" to "CUAG" and corrected a transposition of SEQ ID NOs: 14 and 15 with regards to their respective RNA. Applicants respectfully request reconsideration and withdrawal of the present objection.

Sequence Listing

Enclosed herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a Substitute Sequence Listing to be inserted into the specification as indicated above. The Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance with 37 C.F.R. §§1.821-1.825 is an electronic CRF copy of the Substitute Sequence Listing. The electronic CRF copy of the Substitute Sequence Listing, file "2009-02-20-1254-0321PUS1_ST25.txt", is identical to the paper copy, except that it lacks formatting. In no way do the paper copy nor the electronic CRF copy of the Substitute Sequence Listing introduce new matter into the application.

The Sequence Listing has been updated to correct errors within SEQ ID NOs: 12 and 15. Specifically, 24 nucleotides at the 5' end and 5 nucleotides at the 3' end, which are derived from

the vector backbone sequence of the clone pJFH1, were inadvertently added to SEQ ID NOs: 12 and 15 when they were prepared. Thus, no new matter is introduced by these amendments.

Issue Under 35 U.S.C. § 112, Second Paragraph, Indefiniteness

Claim 5 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants respectfully traverse.

The Examiner asserts that from the language of claim 5, it is unclear to the Examiner if the requirement in part (b) that the RNA has autonomous replication ability and virus particle production ability is intended to apply to both parts ((a) and (b)) of the claim, or if the requirement applies only to subpart (b). Applicants respectfully traverse.

Although Applicants disagree, in order to further prosecution, Applicants have amended claim 5, without prejudice or disclaimer of the subject matter contained therein, to address this issue. Specifically, Applicants amended claim 5(a) to recite "...which has autonomous replication ability and virus particle production ability...." so that the claim language is clear that this requirement is to apply to both parts (a) and (b).

Applicants submit that claim 5 particularly points out and distinctly claims the subject matter which Applicants regard as the invention.

Applicants respectfully request reconsideration and withdrawal of the present rejection.

Issues Under 35 U.S.C § 112, First Paragraph, Written Description

Claims 1-11 and 22 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. The Examiner asserts that the claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor was in possession of the claimed invention at the time the application was filed.

The Examiner asserts that although the present application teaches an HCV genotype 2a full length replicon (with examples of a limited number of mutant forms), the application does not disclose what structures or sequences correlate with the operability of HCV replicons in general, either for replication or for the production of viral particles. Additionally, the Examiner asserts that the application does not provide any examples of replicons of other genotypes of HCV (See the page 5-8 of the Office Action). Applicants respectfully traverse.

Although Applicants disagree, in order to further prosecution, Applicants have amended claims 1, 5 and 22, without prejudice or disclaimer of the subject matter contained therein, to address the above issues. Specifically, Applicants amended claim 1 to provide specific structure to the replicon RNA by limiting the 5' UTR, core, El, E2, NS2, NS3, NS4A, NS4B, NS5A NS5B, and 3'UTR sequences to the specific sequences (SEQ ID NOs: 1-11) from the full length genomic RNA of HCV genotype 2a of strain JFH1 (SEQ ID. NO: 12). The above nucleotide sequences were incorporated from claim 4, now cancelled.

With regards to claim 5, Applicants amended the claim to provide structural elements within the replicon RNA. Further claim 5 was amended to indicate that the RNA within (a) comprises the nucleotide sequence of SEQ ID NO: 13 and has autonomous replication ability

and virus particle production ability, while part (b) the RNA comprises the nucleotide sequence of SEQ ID NO: 13 with deletions, substitutions, or additions limited to 1 to 30 nucleotides. Part (b) also has both autonomous replication ability and virus particle production ability.

Concerning claim 22, Applicants amended the claim to indicate that the isolated RNA comprises the nucleotide sequence shown in SEQ ID NO: 12 (claim 23, presently withdrawn, was amended in the same manner as claim 22).

Finally, Applicants also provide new claim 27 for the Examiner's consideration. This claim is similar to original claim 5, but is further limiting part (b) to 1 to 10 nucleotides.

Applicants submit that the pending claims contain subject matter that is described in the specification in such a way as to reasonably convey to a skilled artisan that the inventor was in possession of the claimed invention at the time the application was filed.

Applicants respectfully request reconsideration, and subsequent withdrawal of the present rejection.

Issues Under 35 U.S.C. § 102(b), Anticipation

The following rejections under 35 U.S.C. § 102(b) were presented by the Examiner.

Claim 5 stands rejected under 35 U.S.C. § 102(b) as anticipated by Kato *et al.*, "*Efficient Replication of the Genotype 2a Hepatitis C Virus Subgenomic Replicon*," Gastroenterology, Volume 125, pp. 1808-17 (hereinafter "Kato") (see the page 8-9 of the Office Action). The Examiner asserts that since the claim does not require that the replicon RNA comprise the full sequence of SEQ ID NO: 13, nor does the claim require that the replicon RNA encodes the full-

length HCV 2a polyprotein, the claim therefore reads on a subgenomic replicon of HCV. The Examiner asserts that Kato teaches a subgenomic replicon of HCV 2a.

Claims 5 and 22 stand rejected under 35 U.S.C. § 102(b) as anticipated by Blanchard *et al.*, "*Hepatitis C Virus-Like Particle Morphogenesis*," J. Virology, Vol. 76, No. 8, pp. 4073-79, (hereinafter "Blanchard") (See page 9 of the Office Action). The Examiner asserts that Blanchard teaches an RNA replicon that autonomously replicates, and produces, a virus-like particle. The Examiner also asserts that the replicon is disclosed as the pSFV1 replicon, a portion of the sequence of which is provided (using DNA sequence) in Ciccarone *et al.*, (Focus 15:103-105, at 104, Figure 2). The Examiner suggests that since the claims do not specify the type of viral particles to be produced, or require the presence of the full-length of SEQ ID NO: 12 or 13, or set a minimum length of the sequences from these sequence to be present in the replicons, the Blanchard reference anticipates the indicated claims.

Applicants respectfully traverse the above rejections.

Although Applicants disagree, in order to further prosecution, Applicants have amended claim 5, as described in the previous rejection. Further parts (a) and (b) were amended so the both parts (a) and (b) indicate "the" nucleotide sequence so as to indicate that the replicon has the entire SEQ ID NO: 13 nucleotide sequence.

Additionally, in the same manner, claim 22 was amended to indicate "the" nucleotide sequence so as to indicate that the replicon has the entire SEQ ID NO: 12 nucleotide sequence.

Since the above references are silent regarding a replicon RNA of claim 5 or the method of producing a cell of claim 22, they do not teach all features of the present invention.

Because "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference," each of the cited references cannot be a basis for a rejection under § 102(b). *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicants respectfully request reconsideration and withdrawal of the present rejections.

Issues Under 35 U.S.C. § 103(a), Obviousness

Claims 1-11 and 22 stand rejected under 35 U.S.C. § 103(a) as unpatentable as obvious over Kato in view of Ikeda *et al.*, "*Selectable Subgenomic and Genome-Length Dicistronic RNAs Dereived from an Infectious Molecular Clone of the HCV-N Strain of Hepatitis C Virus Replicate Efficiently in Cultured Huh7 Cells*," Journal of Virology, Volume 76, No. 6., pp. 2997-3006 (hereinafter "Ikeda") and of EMBL AB047639 (See pages 9-11 of the Office Action).

The Examiner asserts that Kato teaches HCV 2a subgenomic replicons and teaches the transfection of the replicons into Huh7 cells. Also, the Examiner asserts that although Kato teaches a subgenomic replicon (which does not include Core, El, or E2 encoding sequences, and therefore does not produce a viral particle), the Kato replicon varies from SEQ ID NO: 13 in lacking the coding sequences for these HCV 2a proteins.

Further, the Examiner asserts, however, that Ikeda indicates that full-length HCV replicons would have been recognized by the skilled artisan as functional equivalents of subgenomic replicons. The Examiner cited the abstract as providing evidence for the above assertion.

Additionally, the Examiner also asserts that the sequence of the HCV genome from which the replicons of SEQ ID NO: 13 and of Kato were made was also known in the art.

Based on the teachings of Kato and Ikeda, the Examiner asserts that it is obvious for the skilled artisan to have made a replicon encoding the full-length HCV 2a genome by adding the structural protein sequences from the EMBL sequence into the subgenomic replicon of Kato. The Examiner concludes that skilled artisans would have made replicons and cells with the functional limitations of claims 3-5 and 22. Applicants respectfully traverse.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), has provided the controlling framework for an obviousness analysis. A proper analysis under § 103(a) requires consideration of the four *Graham* factors of: determining the scope and content of the prior art; ascertaining the differences between the prior art and the claims that are at issue; resolving the level of ordinary skill in the pertinent art; and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467.

M.P.E.P. § 2143 sets forth the guidelines in determining obviousness. But before the Examiner can utilize these guidelines, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*; *supra*. To reject a claim based on the above mentioned guidelines, the Examiner must resolve the *Graham* factual inquiries. MPEP §2143.

If the Examiner resolves the *Graham* factual inquiries, then the Examiner has to provide some rationale for determining obviousness, wherein M.P.E.P. § 2143 sets forth the rationales that were established in *KSR Int'l Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

Applicants respectfully submit that the Examiner has not appropriately resolved the *Graham* factors, including the factors of determining the scope and content of the prior art and

ascertaining the differences between the prior art and the claims that are at issue. Based on the following, Applicants maintain that the above mentioned *Graham* factors actually reside in Applicants' favor. Additionally, Applicants submit that since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides for combining the cited references is improper.

Applicants respectfully submit that the presently claimed invention is distinct from and unobvious over Kato in view of Ikeda.

The instant invention

The present invention relates to a method for efficiently replicating RNA containing full length hepatitis C virus (HCV) genomic sequences and a method for producing HCV virus particles containing full length HCV replicon RNA or full length HCV genomic RNA in a cell culture system. A replicon RNA was constructed having autonomous replication ability and virus particles production ability, using HCV genomic RNA.

Applicants submit that in claims 1-5 and 22, all the 5' UTR, core, El, E2, NS2, NS3, NS4A, NS4B, NS5A, NS5B, and 3'UTR sequences of claim 1 are derived from a full length genomic RNA of HCV genotype 2a, where the full length genomic RNA of HCV genotype 2a has the nucleotide sequence of SEQ ID NO: 12. Applicants contend that a skilled artisan would understand and properly interpret the claim's meaning based upon consideration of the claims with respect to the entire present specification. Applicants also contend that based on the amended claims it is clear that they do not mean that the replicon comprises a sequence from at least one of SEQ ID NOs: 1-13.

Differences between the invention and the prior art

As indicated above, Applicants have provided further amendments that distinguish the present invention from the Kato reference.

Additionally, with regards to Ikeda, the Examiner asserts that that the teachings of Ikeda indicate that full-length HCV replicons would have been recognized by the skilled artisan as functional equivalents of subgenomic replicons. However, Ikeda does not clearly mention this and it appears that it merely describes within the abstract "*Additional selectable, dicistronic RNAs encoding NS2- NS5B, or the full-length HCV polyprotein were also capable of replication and gave rise to G418-resistant cell clones following transfection of Huh 7 cells.*"

Applicants submit that this one fact is found in the HCV genotype 1b of the HCV-N strain, and does not indicate whether full-length HCV replicons are generally (*i.e.*, also in other HCV genotypes such as genotype 2a) functionally equivalent to the subgenomic replicons.

Applicants point out that on page 7 of the Office Action, the Examiner discussed that the art teaches that the construction of HCV replicons for other HCV genotypes have not been successful (Ikeda (1998), Date *et al.*, and Meunier *et al*). Considering the teachings of the art, Ikeda does not indicate that full-length HCV replicons would have been recognized as functional equivalents to that of subgenomic replicons.

Further, as the Examiner discussed in the last paragraph of page 7 of the Office Action, the art had reported that full-length replicons showing to replicate in cells do not appear to produce viral particles (Pietschmann *et al.*).

In contrast, the replicon of the present invention, which was obtained with the full-length genome of the JFH-1 strain (SEQ ID NO: 12), can produce viral particles as well as replicate in cells (see, the Examples within the present specification). The virus particle production ability of the replicon of the present invention is neither taught nor suggested in either Kato or Ikeda.

Applicants respectfully disagree with the Examiner that the present invention would be obvious to the skilled artisan. Applicants submit that a skilled artisan would not have arrived at constructing the claimed replicons based on the full-length genome of JFH-1 strain which also provides virus particle production ability. And as stated in the § 112 rejections, the art is unpredictable. Thus, Applicants contend that the teachings of Kato and Ikeda do not render the claimed inventions obvious and that the present invention as claimed is suitably distinguished over the combination of references cited.

In light of the above presently amended claims and remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the cited references that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the same references are incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established.

With regards to the Ikeda reference, Ikeda does not cure the deficiencies of Kato. Therefore, the combination of Kato and Ikeda is improper. Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established for any of the above claims. Applicants respectfully request reconsideration and subsequent withdrawal of the above rejections.

Obviousness-Type Non-Statutory Double Patenting

Claims 1-5 and 22 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-13 and 21 of co-pending Application No. 10/558,155 in view of Ikeda.

The Examiner asserts that although the claims of the present invention differ from that of the cited co-pending application, since claim 5 does not require that the replicon is a full length replicon, the co-pending claims would anticipate that claim if applied as prior art.

Claim 5 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-8 of co-pending Application No. 11/898,468, and over claim 34 of co-pending application 10/572,476. The Examiner states that although the conflicting claims are not identical, they are not patentably distinct from each other because claim 5 reads on a replicon, including subgenomic replicons, that comprise a sequence found within SEQ ID NO: 13.

The Examiner asserts that co-pending claims of Application No. 11/898,468 read on replicons comprising the sequences of SEQ ID NOs: 2, 5, and 6 of that application, of which at least SEQ ID NO: 2 shares common sequences with present SEQ ID NO: 13. The Examiner also asserts that the SEQ ID NO: 7 referenced in Application No. 10/572,476 includes the sequence of Application No. 11/898,468 of SEQ ID NO: 2. Thus, the Examiner concludes that claims of that application also share sequences with SEQ ID NO: 13.

Applicants respectfully traverse the above provisional rejections.

As indicated above, the Applicants have amended claims 1, 5 and 22 and respectfully submit that the present application is patentably distinct from the above cited co-pending

applications. Otherwise, Applicants request the Examiner to hold the provisional rejections in abeyance until this or one of the other applications issue as a patent. Applicants request reconsideration and withdrawal of the present rejections.

CONCLUSION

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case.

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters within the present application that need to be resolved, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: FEB 23 2009

Respectfully submitted,

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